Genetics Home Reference

Your Guide to Understanding Genetic Conditions

Help Me Understand Genetics

Chapter 2

Genetic Disorders

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Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
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Chapter 2

Genetic Disorders

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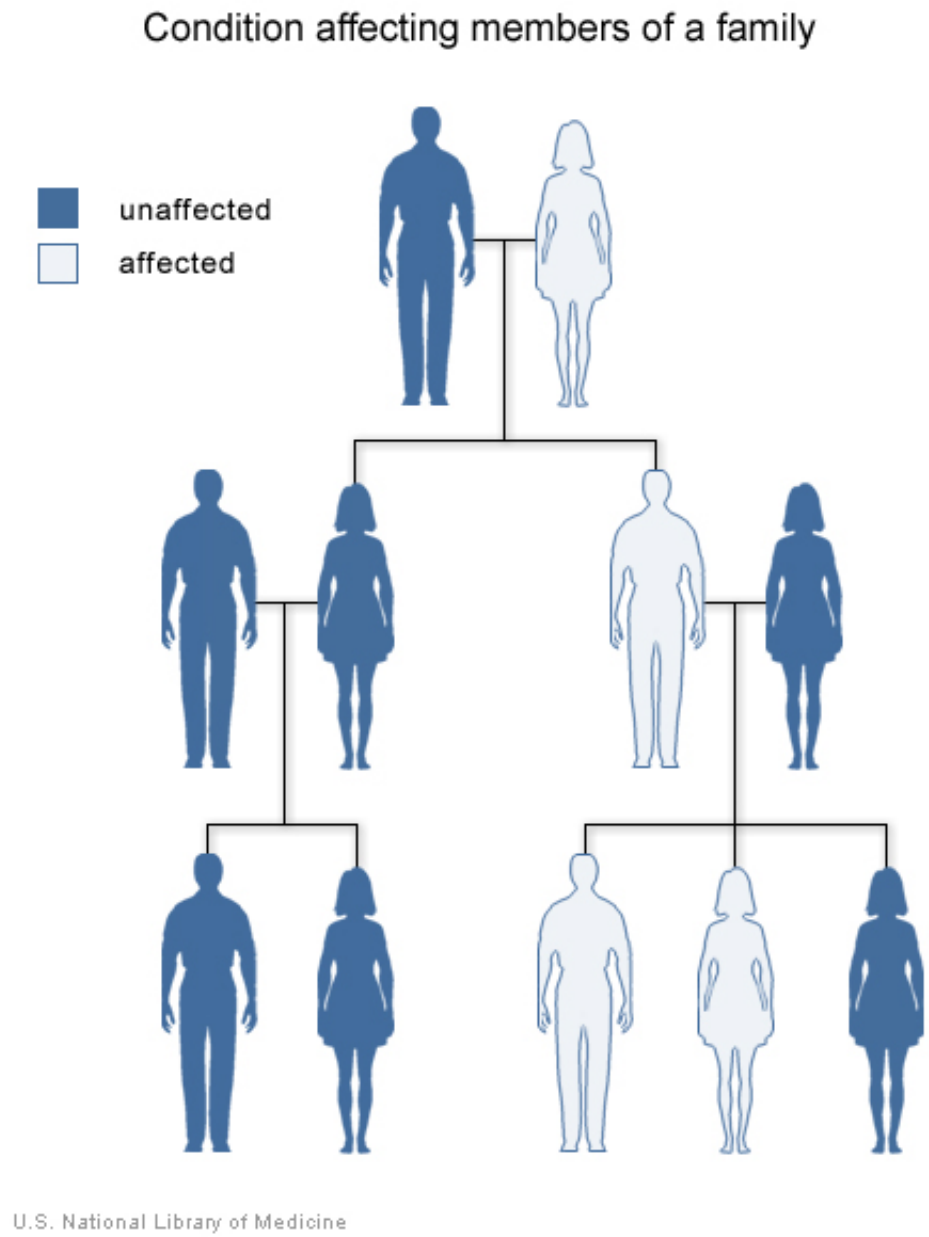
What does it mean if a disorder seems to run in my family?

A particular disorder might be described as “running in a family” if more than one person in the family has the condition. Some disorders that affect multiple family members are caused by gene mutations, which can be inherited (passed down from parent to child). Other conditions that appear to run in families are not inherited. Instead, environmental factors such as dietary habits or a combination of genetic and environmental factors are responsible for these disorders.

It is not always easy to determine whether a condition in a family is inherited. A genetics professional can use a person's family history (a record of health information about a person's immediate and extended family) to help determine whether a disorder has a genetic component.



Some disorders are seen in more than one generation of a family.

For general information about disorders that run in families:

The National Human Genome Research Institute fact sheet Frequently Asked Questions About Genetics (http://www.genome.gov/10001191) offers a general description of genetic disorders. Please refer to the first two questions, “What are genetic disorders?” and “How do I find more information about a specific disorder or learn whether a particular disease has a genetic component?”

The Department of Energy offers a fact sheet called Genetic Disease Information—Pronto! (http://www.ornl.gov/TechResources/Human_Genome/medicine/assist.html)

What is a gene mutation and how do mutations occur?

A gene mutation is a permanent change in the DNA sequence that makes up a gene. Mutations range in size from one DNA base to a large segment of a chromosome.

Gene mutations occur in two ways: they can be inherited from a parent or acquired during a person's lifetime. Mutations that are passed from parent to child are called hereditary mutations or germline mutations (because they are present in the egg and sperm cells, which are also called germ cells). This type of mutation is present throughout a person's life in virtually every cell in the body.

Acquired (or sporadic) mutations, on the other hand, occur in the DNA of individual cells at some time during a person's life. These changes can be caused by environmental factors such as ultraviolet radiation from the sun, or can occur if a mistake is made as DNA copies itself during cell division. Acquired mutations in somatic cells (cells other than sperm and egg cells) cannot be passed on to the next generation. If a mutation occurs in an egg or sperm cell during a person's life, however, there is a chance that the person's children will inherit the mutation.

For more information about mutations:

The National Cancer Institute offers a discussion of hereditary mutations (http://press2.nci.nih.gov/sciencebehind/genetesting/genetesting12.htm) and information about acquired mutations (http://press2.nci.nih.gov/sciencebehind/genetesting/genetesting13.htm).

For additional information about gene mutations, please refer to the following resources from the University of Utah Genetic Science Learning Center:

What is a Mutation? (http://gslc.genetics.utah.edu/units/disorders/mutations/)

How do Mutations Occur? (http://gslc.genetics.utah.edu/units/disorders/sloozeworm/)

How can gene mutations cause disorders?

To function correctly, each cell depends on thousands of proteins to do their jobs in the right places at the right times. Sometimes, gene mutations prevent one or more of these proteins from working properly. By changing a gene's instructions for making a protein, a mutation can cause the protein to malfunction or to be missing entirely. When a mutation alters a protein that plays a critical role in the body, a medical condition can result. A condition caused by mutations in one or more genes is called a genetic disorder.

It is important to note that genes themselves do not cause disease—genetic disorders are caused by mutations that make a gene function improperly. For example, when people say that someone has "the cystic fibrosis gene," they are usually referring to a mutated version of the CFTR gene, which causes the disease. All people, including those without cystic fibrosis, have a version of the CFTR gene.

For more information about mutations and genetic disorders:

The National Cancer Institute provides additional information about how gene mutations can trigger disease. Please refer to the following Web pages:

Gene Mutations and Disease (http://press2.nci.nih.gov/sciencebehind/genetesting/genetesting09.htm)

Altered DNA, Altered Protein (http://press2.nci.nih.gov/sciencebehind/genetesting/genetesting11.htm)

The University of Utah Genetic Science Learning Center also offers a discussion titled How Do Mutations Cause Genetic Disorders? (http://gslc.genetics.utah.edu/units/disorders/proteinrole/)

Do all gene mutations cause disorders?

No; only a small percentage of mutations cause genetic disorders—most have no impact on health. For example, some mutations alter a gene's DNA base sequence but don’t change the function of the protein made by the gene.

Often, gene mutations that could cause a genetic disorder are repaired by certain enzymes before the gene is expressed (makes a protein). Each cell has a number of pathways through which enzymes recognize and repair mistakes in DNA. Because DNA can be damaged or mutated in many ways, the process of DNA repair is an important way in which the body protects itself from disease.

A very small percentage of all mutations actually have a positive effect. These mutations lead to new versions of proteins that help an organism and its future generations better adapt to changes in their environment. For example, a beneficial mutation could result in a protein that protects the organism from a new strain of bacteria.

For more information about DNA repair and the health effects of gene mutations:

The University of Utah Genetic Science Learning Center's page about genetic disorders (http://gslc.genetics.utah.edu/units/disorders/whataregd/) explains why some mutations cause disorders but others do not. (Please refer to the questions in the far right column.)

Additional information about DNA repair is available from the NCBI Science Primer (http://www.ncbi.nlm.nih.gov/About/primer/genetics_cell.html). Scroll down the page to the heading “DNA Repair Mechanisms.”

What kinds of gene mutations are possible?

The DNA sequence of a gene can be altered in a number of ways. Gene mutations have varying effects on health, depending on where they occur and whether they alter the function of essential proteins. The types of mutations include:

Missense mutation (illustration on page 10)

This type of mutation is a change in one DNA base pair that results in the substitution of one amino acid for another in the protein made by a gene.

Nonsense mutation (illustration on page 11)

A nonsense mutation is also a change in one DNA base pair. Instead of substituting one amino acid for another, however, the altered DNA sequence prematurely signals the cell to stop building a protein. This type of mutation results in a shortened protein that may function improperly or not at all.

Insertion (illustration on page 11)

An insertion changes the number of DNA bases in a gene by adding a piece of DNA. As a result, the protein made by the gene may not function properly.

Deletion (illustration on page 12)

A deletion changes the number of DNA bases in a gene by removing a piece of DNA. The deleted DNA may alter the function of the resulting protein.

Duplication (illustration on page 12)

A duplication consists of a piece of DNA that is abnormally copied one or more times. This type of mutation may alter the function of the resulting protein.

Frameshift mutation (illustration on page 13)

This type of mutation occurs when the addition or loss of DNA bases changes a gene's reading frame. A reading frame consists of groups of 3 bases that each code for one amino acid. A frameshift mutation shifts the grouping of these bases and changes the code for amino acids. The resulting protein is usually nonfunctional. Insertions, deletions, and duplications can all be frameshift mutations.

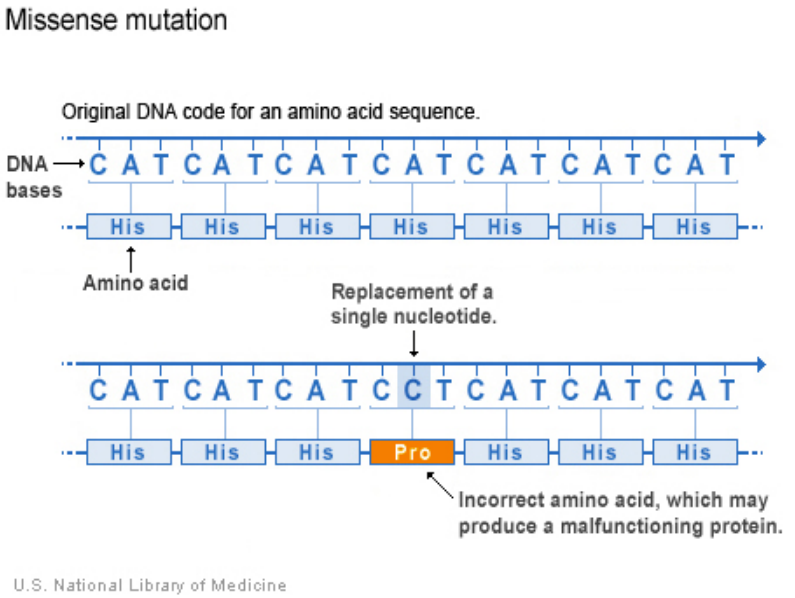
Repeat expansion (illustration on page 13)

Nucleotide repeats are short DNA sequences that are repeated a number of times in a row. For example, a trinucleotide repeat is made up of 3-base-pair sequences, and a tetranucleotide repeat is made up of 4-base-pair sequences. A repeat expansion is a mutation that increases the number of times that the short DNA sequence is repeated. This type of mutation can cause the resulting protein to function improperly.

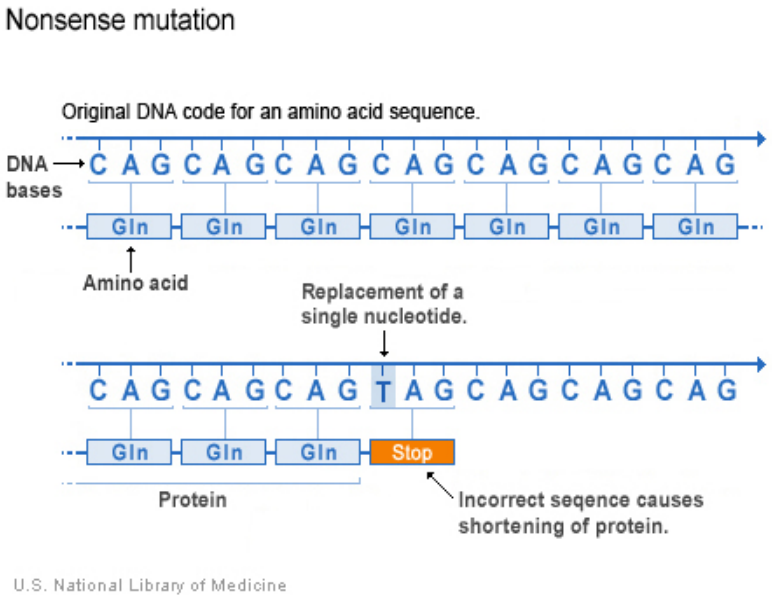
For more information about the types of gene mutations:

The National Human Genome Research Institute offers a Talking Glossary of Genetic Terms (http://www.genome.gov/10002096). This resource includes definitions, diagrams, and detailed audio descriptions of several of the gene mutations listed above.

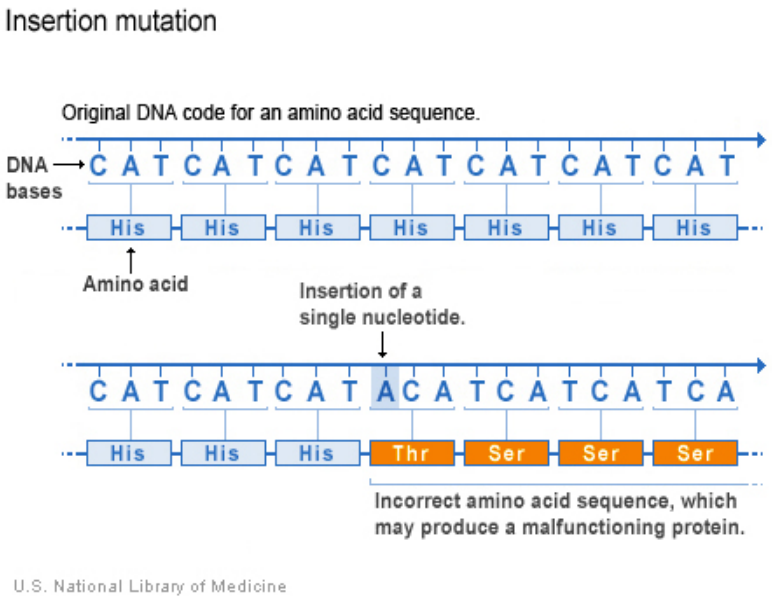
Illustrations: Types of gene mutations



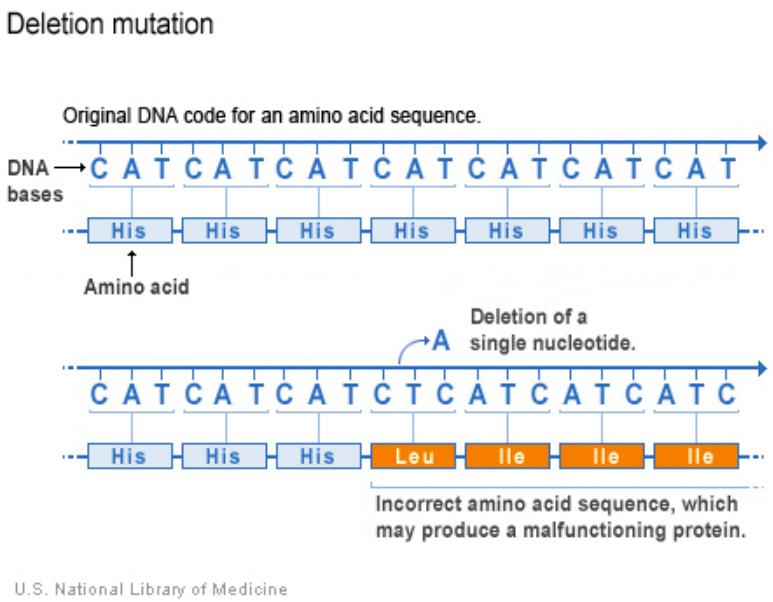
In this example, the nucleotide adenine is replaced by cytosine in the genetic code, introducing an incorrect amino acid into the protein sequence.



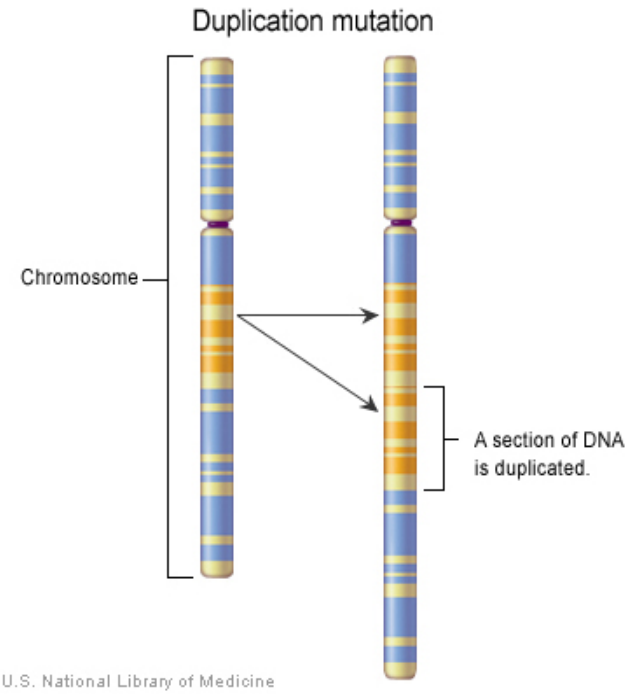
In this example, the nucleotide cytosine is replaced by thymine in the DNA code, signaling the cell to shorten the protein.



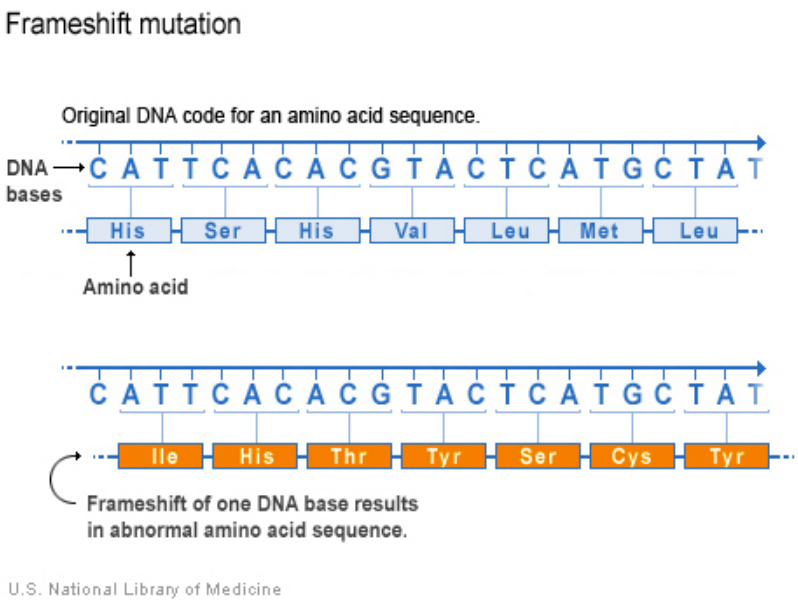
In this example, one nucleotide (adenine) is added in the DNA code, changing the amino acid sequence that follows.



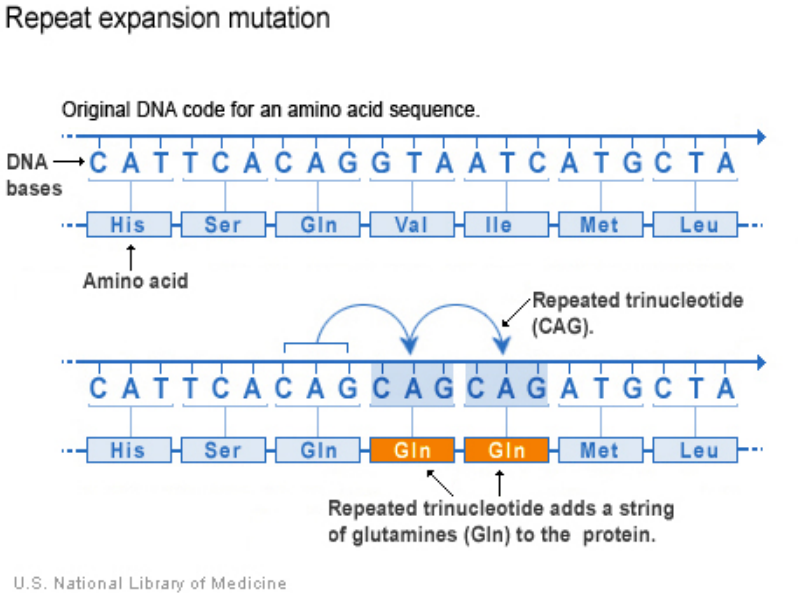
In this example, one nucleotide (adenine) is deleted from the DNA code, changing the amino acid sequence that follows.



A section of DNA is accidentally duplicated when a chromosome is copied.



A frameshift mutation changes the amino acid sequence from the site of the mutation.



In this example, a repeated trinucleotide sequence (CAG) adds a series of the amino acid glutamine to the resulting protein.

What are the different ways in which a genetic condition can be inherited?

Some genetic conditions are caused by mutations in a single gene. These conditions are usually inherited in one of several straightforward patterns, depending on the gene involved:

Inheritance pattern	Description	Examples
Autosomal dominant	Only one mutated copy of the gene is needed for a person to be affected by an autosomal dominant disorder. Each affected person usually has one affected parent (illustration on page 16).	Huntington disease, neurofibromatosis 1
Autosomal recessive	Two copies of the gene must be mutated for a person to be affected by an autosomal recessive disorder. An affected person usually has unaffected parents who each carry a single copy of the mutated gene (and are referred to as carriers) (illustration on page 17).	cystic fibrosis, sickle cell anemia
X-linked dominant	X-linked dominant disorders are caused by mutations in genes on the X chromosome. Only a few disorders have this inheritance pattern. Females are more frequently affected than males, and the chance of passing on an X-linked dominant disorder differs between men (illustration on page 18) and women (illustration on page 19).	X-linked hypophosphatemia
X-linked recessive	X-linked recessive disorders are also caused by mutations in genes on the X chromosome. Males are more frequently affected than females, and the chance of passing on the disorder differs between men (illustration on page 20) and women (illustration on page 21).	hemophilia A, Duchenne muscular dystrophy

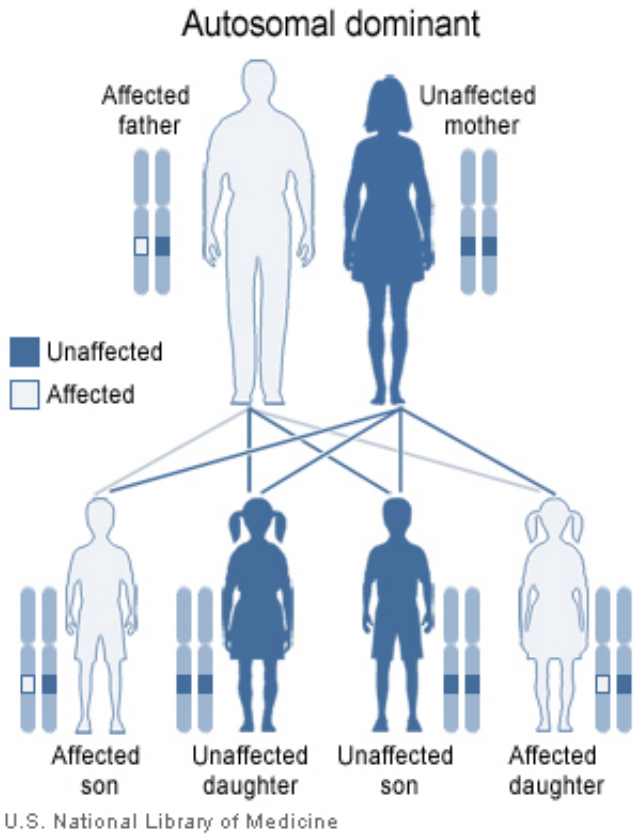
Inheritance pattern	Description	Examples
Mitochondrial	This type of inheritance, also known as maternal inheritance, applies to genes in mitochondrial DNA. (Mitochondria, which are structures in each cell that convert molecules into energy, each contain a small amount of DNA.) Because only egg cells contribute mitochondria to the developing embryo, only females can pass on mitochondrial conditions to their children (illustration on page 22).	Leber's hereditary optic neuropathy (LHON)

Many other disorders are caused by a combination of the effects of multiple genes or by interactions between genes and the environment. Such disorders are more difficult to analyze because their genetic causes are often unclear, and they do not follow the patterns of inheritance described above. Examples of conditions caused by multiple genes or gene/environment interactions include heart disease, diabetes, schizophrenia, and certain types of cancer.

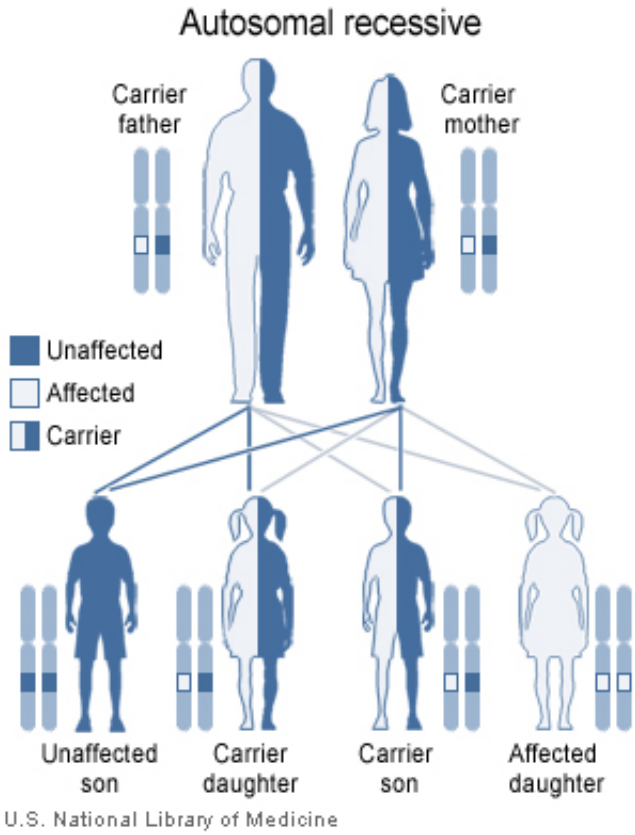
For more information about inheritance patterns:

The Genetics and Public Policy Center provides an introduction to hereditary mutations (http://www.dnapolicy.org/genetics/geneticsAndDisease.jhtml#hered), including their patterns of inheritance.

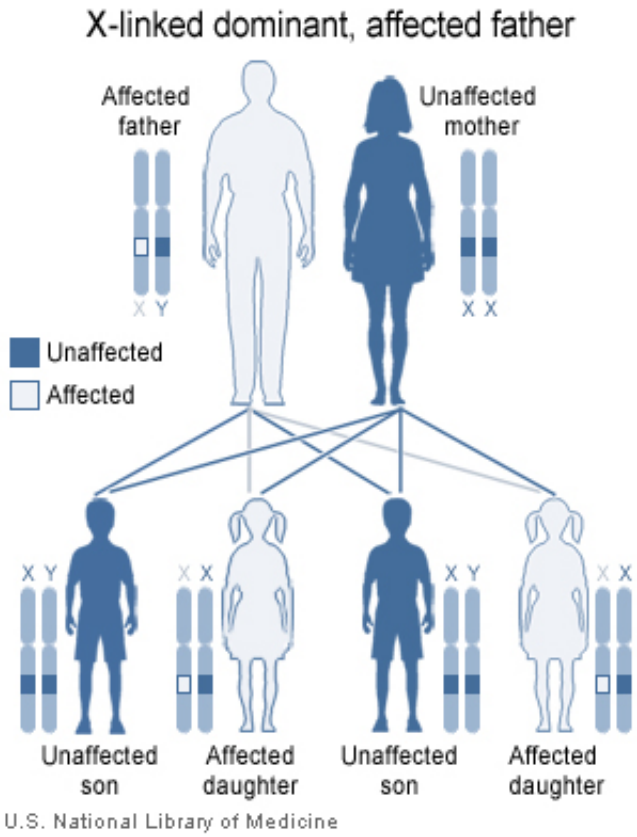
Illustrations: Inheritance patterns



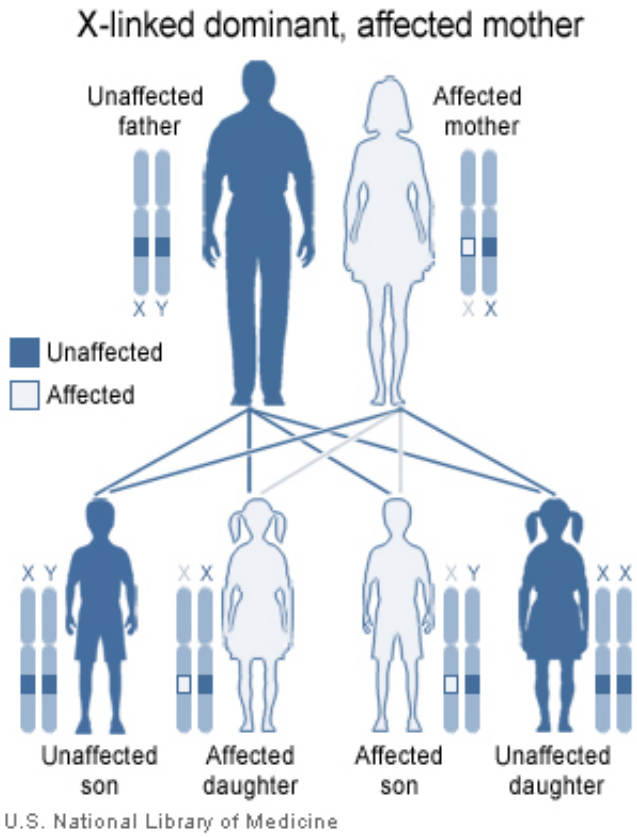
In this example, a man with an autosomal dominant disorder has two affected children and two unaffected children.



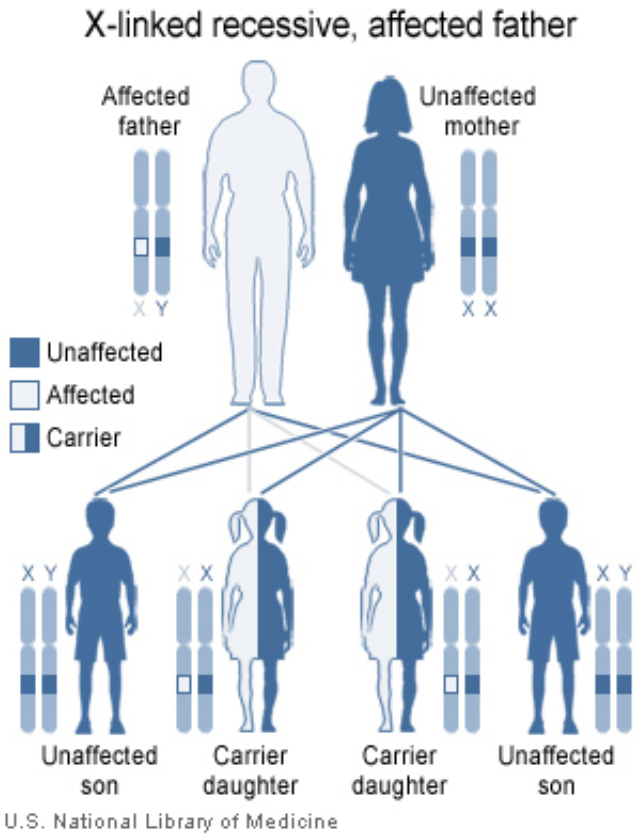
In this example, two unaffected parents each carry one copy of a gene mutation for an autosomal recessive disorder. They have one affected child and three unaffected children, two of which carry one copy of the gene mutation.



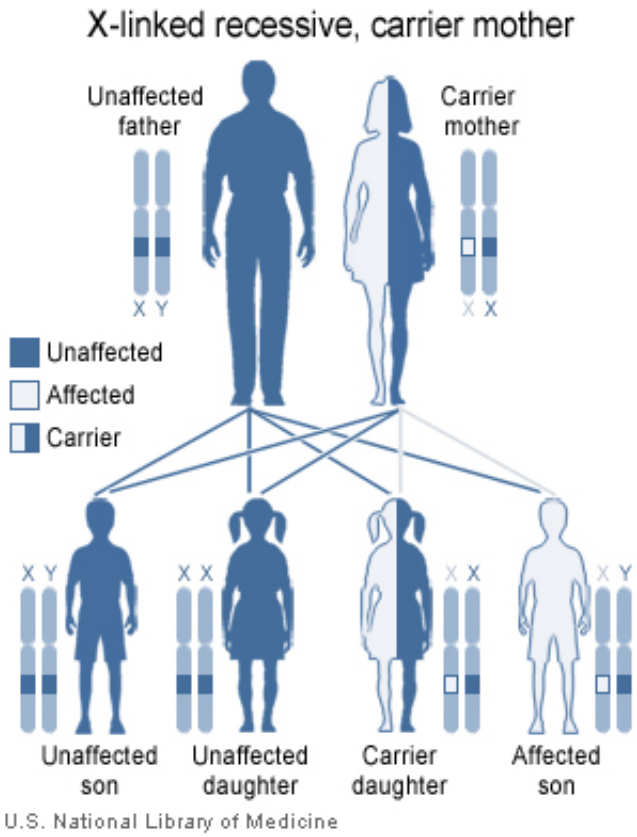
In this example, a man with an X-linked dominant condition has two affected daughters and two unaffected sons.



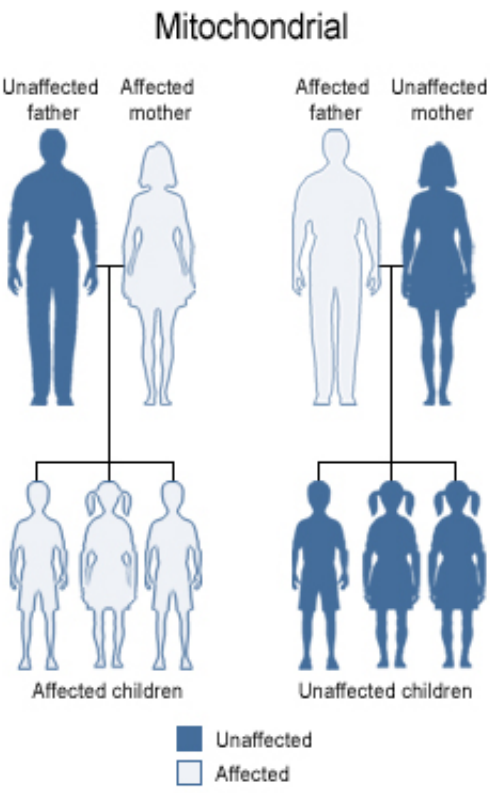
In this example, a woman with an X-linked dominant condition has an affected daughter, an affected son, an unaffected daughter, and an unaffected son.



In this example, a man with an X-linked recessive condition has two unaffected daughters who each carry one copy of the gene mutation, and two unaffected sons who do not have the mutation.



In this example, an unaffected woman carries one copy of a gene mutation for an X-linked recessive disorder. She has an affected son, an unaffected daughter who carries one copy of the mutation, and two unaffected children who do not have the mutation.



U.S. National Library of Medicine

In one family, a woman with a mitochondrial disorder and her unaffected husband have only affected children. In another family, a man with a mitochondrial condition and his unaffected wife have no affected children.

If a genetic disorder runs in my family, what are the chances that my children will have the condition?

When a genetic disorder is diagnosed in a family, family members often want to know the likelihood that they or their children will develop the condition. This can be difficult to predict in some cases because many factors influence a person's chances. One important factor is how the condition is inherited. For example:

- A person affected by an autosomal dominant disorder has a 50-percent chance of passing the mutated gene to each child. There is also a 50-percent chance that a child will not inherit the mutated gene (illustration on page 16).
- For an autosomal recessive disorder, two unaffected people who each carry one copy of the mutated gene (carriers) have a 25-percent chance with each pregnancy of having a child affected by the disorder. There is a 75-percent chance with each pregnancy that a child will be unaffected (illustration on page 17).
- The chance of passing on an X-linked dominant condition differs between men and women because men have one X and one Y chromosome, while women have two X chromosomes. A man passes on his Y chromosome to all of his sons and his X chromosome to all of his daughters. Therefore, the sons of a man with an X-linked dominant disorder will not be affected, and his daughters will all inherit the condition (illustration on page 18). A woman passes on one or the other of her X chromosomes to each child. Therefore, a woman with an X-linked dominant disorder has a 50-percent chance of having an affected daughter or son with each pregnancy (illustration on page 19).
- Because of the difference in sex chromosomes, the probability of passing on an X-linked recessive disorder also differs between men and women. The sons of a man with an X-linked recessive disorder will not be affected, and his daughters will carry one copy of the mutated gene (illustration on page 20). With each pregnancy, a woman who carries an X-linked recessive disorder has a 50-percent chance of having sons who are affected and a 50-percent chance of having daughters who carry one copy of the mutated gene (illustration on page 21).

It is important to note that the chance of passing on a genetic condition applies equally to each pregnancy. For example, if a couple has a child with an autosomal recessive disorder, the chance of having another child with the disorder is still 25 percent (or

1 in 4). Having one child with a disorder does not "protect" future children from inheriting the condition. Conversely, having a child without the condition does not mean that future children will definitely be affected.

Although the chances of inheriting a genetic condition appear straightforward, in some cases factors such as a person's family history and the results of genetic testing can modify those chances. In addition, some people with a disease-causing mutation never develop any health problems or may experience only mild symptoms of the disorder. If a disease that runs in a family does not have a clear-cut inheritance pattern, predicting the likelihood that a person will develop the condition can be particularly difficult.

Because estimating the chance of developing or passing on a genetic disorder can be complex, genetics professionals can help people understand these chances and make informed decisions about their health.

For more information about passing on a genetic disorder in a family:

The National Library of Medicine MedlinePlus web site offers information about the chance of developing a genetic disorder on the basis of its inheritance pattern. Scroll down to the section "Statistical Chances of Inheriting a Trait" for each of the following inheritance patterns:

Autosomal dominant (http://www.nlm.nih.gov/medlineplus/ency/article/002049.htm)

Autosomal recessive (http://www.nlm.nih.gov/medlineplus/ency/article/002052.htm)

X-linked dominant (http://www.nlm.nih.gov/medlineplus/ency/article/002050.htm)

X-linked recessive (http://www.nlm.nih.gov/medlineplus/ency/article/002051.htm)

Can changes in chromosomes cause disorders?

Yes; changes that affect entire chromosomes or large segments of chromosomes can cause problems with growth, development, and function of the body's systems. These changes can affect many genes along the chromosome and alter the proteins made by those genes. Conditions caused by a change in the number or structure of chromosomes are known as chromosomal disorders. Many chromosomal disorders are not inherited.

Human cells normally contain 23 pairs of chromosomes, for a total of 46 in each cell. A change in the number of chromosomes leads to a chromosomal disorder. A gain or loss of chromosomes from the normal 46 is called aneuploidy. Down syndrome is an example of a condition caused by aneuploidy—people with Down syndrome have an extra copy of chromosome 21, for a total of 47 chromosomes in each cell.

Chromosomal disorders can also be caused by changes in chromosome structure. These changes are caused by the breakage and reunion of chromosome segments when an egg or sperm cell is formed. Pieces of DNA can be rearranged within one chromosome, or transferred between two or more chromosomes. The effects of structural changes depend on their size and location. Some disorders caused by changes in chromosome structure can be passed from parent to child.

For more information about chromosomal disorders:

Chromosome Deletion Outreach offers a fact sheet on this topic titled Introduction to Chromosome Abnormalities (http://www.chromodisorder.org/intro.htm).

Georgetown University's Human Genome Education Model Project II provides a fact sheet (http://www.georgetown.edu/research/gucdc/hugem/fs12.htm) about chromosomal disorders and their causes.

The Genetics and Public Policy center also offers an overview of chromosomal mutations (http://www.dnapolicy.org/genetics/geneticsAndDisease.jhtml#chromo).

Why are some genetic conditions more common in particular ethnic groups?

Some genetic disorders are more likely to occur among people who trace their ancestry to a particular geographic area. People in an ethnic group often share certain versions of their genes, which have been passed down from common ancestors. If one of these shared genes contains a disease-causing mutation, a particular genetic disorder may be more frequently seen in the group.

Examples of genetic conditions that are more common in particular ethnic groups are sickle cell anemia, which is more common in people of African, African-American, or Mediterranean heritage; and Tay-Sachs disease, which is more likely to occur among people of Ashkenazi (eastern and central European) Jewish or French Canadian ancestry. It is important to note, however, that these disorders can occur in any ethnic group.

For more information about genetic disorders that are more common in certain groups:

The National Institute of General Medical Sciences (NIGMS) fact sheet Genes & Populations (http://www.nigms.nih.gov/news/science_ed/genepop/faq.html) offers additional discussion on this topic. Scroll down to the question “Why do researchers sometimes study ethnic and racial groups?”

What information about a genetic condition can statistics provide?

Statistical data can provide general information about how common a condition is, how many people have the condition, or how likely it is that a person will develop the condition. Statistics are not personalized, however—they offer estimates based on groups of people. By taking into account a person's family history, medical history, and other factors, a genetics professional can help interpret what statistics mean for a particular patient.

Some statistical terms are commonly used when describing genetic conditions and other disorders. These terms include:

Statistical term	Description	Examples
Incidence	The incidence of a gene mutation or a genetic disorder is the number of people who are born with the mutation or disorder in a specified group per year. Incidence is often written in the form “1 in [a number]” or as a total number of live births.	About 1 in 200,000 people in the United States are born with syndrome A each year. An estimated 15,000 infants with syndrome B were born last year worldwide.
Prevalence	The prevalence of a gene mutation or a genetic disorder is the total number of people of any age who have the mutation or disorder in a specified group at a given time. This includes both newly diagnosed and pre-existing cases. Prevalence is often written in the form “1 in [a number]” or as a total number of people who have a condition.	Approximately 1 in 100,000 people in the United States have syndrome A at the present time. About 100,000 children worldwide currently have syndrome B.
Mortality	Mortality is the number of deaths from a particular disorder occurring in a specified group per year. Mortality is usually expressed as a total number of deaths.	An estimated 12,000 people worldwide died from syndrome C in 2002.

Statistical term	Description	Examples
Lifetime risk	Lifetime risk is the average risk of developing a particular disorder at some point during a lifetime. Lifetime risk is often written as a percentage or as “1 in [a number].” It is important to remember that the risk per year or per decade is much lower than the lifetime risk. In addition, other factors may increase or decrease a person's risk as compared with the average.	Approximately 1 percent of people in the United States develop disorder D during their lifetimes. The lifetime risk of developing disorder D is 1 in 100.

For more information about interpreting statistics:

The National Alliance of Breast Cancer Organizations (NABCO) offers a fact sheet titled Comments on Putting Cancer Statistics in Context (http://www.nabco.org/index.php/index.php/138). This resource lists the uses and limitations of cancer statistics. Although the fact sheet focuses on cancer, information about interpreting medical statistics can also apply to other disorders.

How are genetic conditions and genes named?

Naming genetic conditions

Genetic conditions are not named in one standard way (unlike genes, which are given an official name and symbol by a formal committee). Doctors who treat families with a particular disorder are often the first to propose a name for the condition. Expert working groups may later revise the name to improve its usefulness. Naming is important because it allows accurate and effective communication about particular conditions, which will ultimately help researchers find new approaches to treatment.

Disorder names are often derived from one or a combination of sources:

- The basic genetic or biochemical defect that causes the condition (for example, alpha-1 antitrypsin deficiency);
- One or more major signs or symptoms of the disorder (for example, sickle cell anemia);
- The parts of the body affected by the condition (for example, retinoblastoma);
- The name of a physician or researcher, often the first person to describe the disorder (for example, Marfan syndrome, which was named after Dr. Antoine Bernard-Jean Marfan);
- A geographic area (for example, familial Mediterranean fever, which occurs mainly in populations bordering the Mediterranean Sea); or
- The name of a patient or family with the condition (for example, amyotrophic lateral sclerosis, which is also called Lou Gehrig disease after a famous baseball player who had the condition).

Disorders named after a specific person or place are called eponyms. There is debate as to whether the possessive form (e.g., Alzheimer's disease) or the nonpossessive form (Alzheimer disease) of eponyms is preferred. As a rule, medical geneticists use the nonpossessive form, and this form may become the standard for doctors in all fields of medicine. Genetics Home Reference uses the nonpossessive form of eponyms.

Genetics Home Reference consults with experts in the field of medical genetics to provide the current, most accurate name for each disorder. Alternate names are included as synonyms.

Naming genes

The HUGO Gene Nomenclature Committee (http://www.gene.ucl.ac.uk/nomenclature/) (HGNC) designates an official name and symbol (an abbreviation of

the name) for each known human gene. Some official gene names include additional information in parentheses, such as related genetic conditions, subtypes of a condition, or inheritance pattern. The HGNC is a non-profit organization funded by the U.K. Medical Research Council and the U.S. National Institutes of Health. The Committee has named more than 13,000 of the estimated 30,000 to 40,000 genes in the human genome.

During the research process, genes often acquire several alternate names and symbols. Different researchers investigating the same gene may each give the gene a different name, which can cause confusion. The HGNC assigns a unique name and symbol to each human gene, which allows effective organization of genes in large databanks, aiding the advancement of research. To access the HGNC's guidelines for naming human genes, click on “Guidelines” from the HGNC home page (http://www.gene.ucl.ac.uk/nomenclature/).

Genetics Home Reference describes genes using the HGNC’s official gene names and gene symbols. Genetics Home Reference frequently presents the symbol and name separated with a colon (for example, FGFR4: fibroblast growth factor receptor 4).

Genetics Home Reference
Your Guide to Understanding Genetic Conditions

http://ghr.nlm.nih.gov/

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U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services

Help Me Understand Genetics

Chapter	Last Comprehensive Review
Genetic Disorders	January 2003

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